

Evaluation of the child with recurrent wheezing

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Activity Objectives

1. To identify features in a clinical presentation suggestive of a non-asthma cause of wheezing.
2. To apply knowledge of the differential diagnosis of wheezing in childhood to formulate a diagnostic strategy.
3. To distinguish a vascular ring from asthma as a cause of wheezing in a school-age child.

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CLINICAL VIGNETTE

An 8-year-old girl presents for evaluation of monthly episodes since infancy of wheezing, cough (often croupy), shortness of breath, and “rattling in the chest” that are generally accompanied by fever. Symptoms initially occurred in the setting of acute respiratory tract infections, and treatment with inhaled bronchodilators and systemic corticosteroids typically provided substantial clinical improvement. However, more recently, she reports exertional dyspnea and persistent cough with minimal improvement despite treatment with inhaled bronchodilators, daily use of low-dose inhaled corticosteroids, and a recent short course of systemic corticosteroids. She has no prior history of pneumonia, recurrent otitis media, sinusitis, or eczema. There were no perinatal complications. The family history is negative for atopic disease and cystic fibrosis. Physical examination was notable for weight and height between the 75th and 90th percentiles. Her respiratory rate was 20 breaths/min, and oxygen saturation was 98% while

breathing room air. She had a nonproductive cough with no signs of respiratory distress. High-pitched expiratory wheeze was noted over the right middle and left lower lobe areas. The results of the cardiac examination were normal. No digital clubbing was noted. Spirometry (see Fig E1 in this article’s Online Repository at www.jacionline.org) revealed mild intrathoracic airflow obstruction (as evidenced by a reduced FEV₁/forced vital capacity ratio) without response to bronchodilator.

Given the presence of symptomatology since infancy and airflow obstruction on spirometry, a chest radiograph (see Fig E2, A, in this article’s Online Repository at www.jacionline.org) was obtained that demonstrated clear lung fields with evidence of a vascular ring with a right-sided aortic arch and posterior tracheal narrowing. This finding led to performance of a barium swallow (see Fig E2, B), which demonstrated a right-sided aortic arch and posterior impression of the esophagus caused by external compression by a vascular ring. Computed tomography confirmed a right-sided aortic arch with an aberrant left subclavian artery. Percutaneous skin testing revealed positive reactions to several molds, cat pelt, and birch mix. She underwent surgical division of a vascular ring, with intraoperative bronchoscopy demonstrating distal tracheal flattening anteriorly. After the procedure, her symptoms resolved completely, and all asthma medications were discontinued without recurrence of symptoms.

The full version of this article, including a review of relevant issues to be considered, can be found online at www.jacionline.org. If you wish to receive CME or MOC credit for the article, please see the instructions above.

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REVIEW

Although asthma is the condition most commonly associated with wheezing, the high prevalence of wheezing as a common presenting complaint requires consideration of a broad and age-dependent differential diagnosis (Table E1). Wheezing might be an isolated symptom or might be accompanied by cough, shortness of breath (either with or without exertion), chest tightness, and/or air hunger.

Definition of wheezing

The classical definition of wheeze is a musical, high-pitched, airway-derived noise detectable during exhalation and resulting from airway obstruction. Unfortunately, although this definition is well known to medical personnel, parents and patients often use the term wheeze to describe a multitude of respiratory symptoms that are not actual wheezes.^{E1-E3} Thus it is incumbent that the provider clarify specifically what sounds or other features are present when the history includes the term wheezing to confirm or refute wheezing as the appropriate descriptor of the symptom under consideration. Stridor, or an inspiratory noise associated with acute extrathoracic/upper airway obstruction, is often confused with wheezing, and its presence prompts consideration of an alternate differential diagnosis.

Wheezing in the preschool-aged child

The younger the child, the broader the differential diagnosis, highlighting the importance of a higher index of suspicion for other causes of wheezing in preschool-aged children. In young children, wheezing is often a manifestation of an acute respiratory tract infection, including viral infections, such as bronchiolitis, caused by respiratory syncytial virus, rhinovirus, and others, as well as other airway infections with typical (*Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae*) and atypical (*Mycobacteria tuberculosis*) organisms. Infection-triggered wheezing can occur in the previously healthy child (often referred to as bronchiolitis) or can cause an acute wheezing exacerbation in children with prior wheezing or other conditions predisposing to recurrent wheeze.

Wheezing during infancy and the preschool years might be the result of anatomic anomalies, such as airway malacia (laryngomalacia, tracheomalacia, and/or bronchomalacia), and is often accompanied by noisy respirations and poor response to bronchodilators and corticosteroids. Wheezing can result from extrinsic impingement of the airway by vascular (vascular ring/sling) or other thoracic (bronchogenic cyst, tumor, lymphadenopathy, and cardiomegaly) structures. Lesions within the airway can produce wheezing, such as laryngeal and tracheal webs. Gastroesophageal reflux is common in infancy and might be associated with chronic or recurrent respiratory symptoms, including wheezing,^{E4,E5} although there remains uncertainty as to whether gastroesophageal reflux is actually causative of wheezing in childhood or represents the unrelated coexistence of 2 relatively common problems (wheezing and gastroesophageal reflux).^{E6} Aspiration can produce airway obstruction and wheezing, as occurs after acute aspiration of a foreign body or chronic aspiration caused by a tracheoesophageal fistula or direct aspiration of oral or gastric secretions. Greater than 90% of acute foreign body aspiration events have an acute choking episode followed by coughing, wheezing, and/or stridor, whereas up to 10% of children with aspiration events have negative or doubtful

histories.^{E7} Cystic fibrosis often presents with recurrent cough and wheeze that is frequently (but not always) accompanied by gastrointestinal symptoms (steatorrhea) and poor weight gain. Primary ciliary dyskinesia can present with a history of neonatal respiratory distress followed by the development of recurrent cough and wheeze and chronic purulent otitis media. Congestive heart failure can produce “cardiogenic wheezing.” Among infants born prematurely, especially those with very low birth weight, prolonged mechanical ventilation, or supplemental oxygen supplementation, chronic lung disease of prematurity or bronchopulmonary dysplasia should be considered, which can be accompanied by airway hyperreactivity and might predispose the patient to a subsequent asthma diagnosis.^{E8}

Wheezing in school-aged children

The differential diagnosis of wheezing in school-aged children does not differ substantially from that in the preschool-aged group, except that many of the congenital conditions become less likely to present later in childhood. As children age beyond the preschool years, the index of suspicion of anatomic causes for wheezing decreases, but as noted in the Clinical vignette, it does not entirely vanish. Foreign body aspiration with retention of the foreign body becomes less likely after the age of 5 years, with fewer than 15% of foreign body aspiration events occurring in children older than 5 years. Infection remains a common cause of acute wheezing in this age group, with rhinovirus infection serving as a common trigger. Bronchiectasis, either primary or secondary to cystic fibrosis, primary ciliary dyskinesia, chronic/recurrent aspiration, and recurrent or persistent infection with or without immunodeficiency can also present with wheeze, often accompanied by productive cough.

Wheezing in adolescents

During the adolescent years, asthma remains the most common cause of recurrent wheezing. However, the new onset of wheezing during adolescence is unusual, and when wheezing is reported *de novo* in this age group, consideration of other diagnostic possibilities is essential. Most episodes of acute wheezing in adolescence are due to acute respiratory tract infections caused by viral, *Mycoplasma pneumoniae*, or bacterial infections. Recurrent episodes of wheezing without a clinical response to bronchodilator or other asthma-targeted therapies, especially with exercise or stressful situations, should prompt consideration of paradoxical vocal cord movement (vocal cord dysfunction). Patients with vocal cord dysfunction often have high-pitched inspiratory stridor caused by vocal cord adduction during inspiration. Focal airway narrowing/obstruction secondary to tumors or bronchogenic cysts might produce wheeze.

Evaluation of the child with recurrent wheezing

As highlighted by the differential diagnostic approach above, a detailed and accurate history and physical examination often provides clues to allow for prioritization of diagnostic possibilities.

First-tier evaluation of the child with recurrent wheeze should include a chest radiograph to evaluate for infiltrates, masses, great vessel abnormalities, radio-opaque retained foreign body, and signs of asymmetry.

Spirometry is helpful in the evaluation of wheezing, with reversible airflow obstruction being highly suggestive of asthma.

However, most children with asthma have FEV₁ percent predicted values within the normal range.^{E9} The presence of a low FEV₁/forced vital capacity ratio is indicative of intrathoracic airflow obstruction, which can be seen in patients with asthma and most other disorders associated with diffuse lower airway inflammation, including cystic fibrosis, bronchiectasis, and primary ciliary dyskinesia. Response to administration of a short-acting β_2 -adrenergic agonist might result in improvement in FEV₁, but many children with asthma also do not demonstrate a substantial ($\geq 12\%$) response to bronchodilator.^{E10} Spirometry also provides both inspiratory and expiratory flow-volume loops, which are helpful in detecting other types of airflow obstruction. Fixed airway obstruction, as seen with a mediastinal mass resulting in extrinsic airway compression, will cause abnormalities of both the inspiratory and expiratory loops. Extrathoracic airflow obstruction, which is detectable as flattening or blunting of the inspiratory loop, is suggestive of vocal cord dysfunction. Bronchoprovocation testing with methacholine, mannitol, cold air, and/or exercise might elicit evidence of airway hyperreactivity.

Sweat chloride analysis with pilocarpine iontophoresis is a very sensitive and specific test for cystic fibrosis, but reports of cases of cystic fibrosis in the setting of normal sweat chloride concentrations remind the physician that genetic testing for mutations in the cystic fibrosis transmembrane regulator gene might be required if cystic fibrosis is suspected despite a normal sweat chloride concentration.

Direct visualization of the airway with fiberoptic bronchoscopy allows for detection of lesions (including laryngeal and tracheal webs), airway malacia, and retained foreign body, as well as obtaining samples for culture and examination of the ciliary microstructure and function. Upper airway examination by means of laryngoscopy might allow for visualization of paradoxical vocal cord movement consistent with vocal cord dysfunction.

Barium esophography might demonstrate a filling defect caused by a vascular ring, whereas a swallow study might disclose macroaspiration. Chest computed tomography allows for detection of thoracic masses, adenopathy, bronchiectasis, and the definition of vascular structures. Evaluation of immune competence might disclose an immune deficiency that predisposes the child to recurrent infections.

Allergic sensitization is common in childhood asthma, and evidence of this in young children with recurrent wheeze increases the likelihood that wheezing will continue through the early school years, increasing the appropriateness of an asthma diagnosis in the preschool-aged group. Thus assessment of evidence of sensitization to common inhalant (and rarely food) allergens by means of skin testing or *in vitro* allergen-specific IgE determination should be part of the evaluation of the child with recurrent wheeze.

The Asthma Predictive Index (API) is a clinical tool that allows for identification of children at the highest risk for persistent wheeze at school age.^{E11,E12} To have a positive API, a child must wheeze before age 3 years and have either 1 of 2 major criteria (parental asthma or personal atopic dermatitis) or 2 of 3 minor criteria (allergic rhinitis, eosinophilia $\geq 4\%$, or wheezing unrelated to colds). Children who wheezed frequently before age 3 years and had a positive API at age 3 years were nearly 10 times more likely to have active asthma at age 6 years and nearly 6 times more likely to have active asthma at age 13 years than children with a negative API. Even children with only 1 wheezing episode before age 3

years were 2.6 to 5.5 times more likely to have persistent asthma at ages 6 and 13 years, respectively, if their APIs were positive. Thus this index can be used to guide caregivers and clinicians as to the likely course of a child's subsequent wheezing.

THE CASE REVISITED

The exploration for alternative diagnoses other than asthma in an 8-year-old child with recurrent lower respiratory tract symptoms since infancy with a historical response to bronchodilators and corticosteroids resulted in identification of a vascular ring caused by a right-sided aortic arch with an aberrant left subclavian artery. This case highlights the importance of consideration of a broad differential diagnosis, especially given the presence of symptoms since infancy and the change in symptom pattern shortly preceding subspecialist evaluation. Identification of this condition at the age of 8 years was relatively late, which is unusual but has been reported.^{E13} Most often, vascular rings present within the first 6 months of life with stridor, wheezing, or both.^{E14} Other presenting symptoms might include vomiting, feeding difficulties, or recurrent chest infections. Although the chest radiographic finding of a right-sided aortic arch was highly suggestive in this case, this finding is often not present and should not preclude further evaluation. Barium esophography identifies esophageal indentation in more than 90% of cases, whereas echocardiography identifies these vascular abnormalities in approximately 50% of cases.^{E14} Computed tomography and magnetic resonance imaging are both very effective in defining anatomy and can aid in planning for surgical correction. In the case presented, the appropriate identification of this congenital anomaly led to surgical correction, symptom resolution, and discontinuation of asthma medications.

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| | Pre-Bronchodilator | Post-Bronchodilator | % Change |
|------------------------------------|--------------------|---------------------|----------|
| FVC (% predicted) | 102 | 103 | 1 |
| FEV ₁ (% predicted) | 84 | 87 | 3 |
| FEV ₁ /FVC (%) | 73 | 75 | |
| FEF ₂₅₋₇₅ (% predicted) | 49 | 58 | 18 |

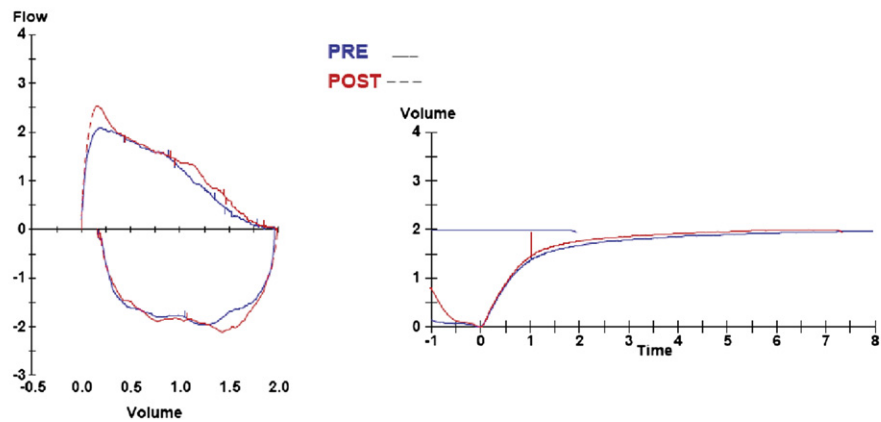


FIG E1. Spirometry revealed mild intrathoracic airflow obstruction without response to bronchodilator. FVC, Forced vital capacity.

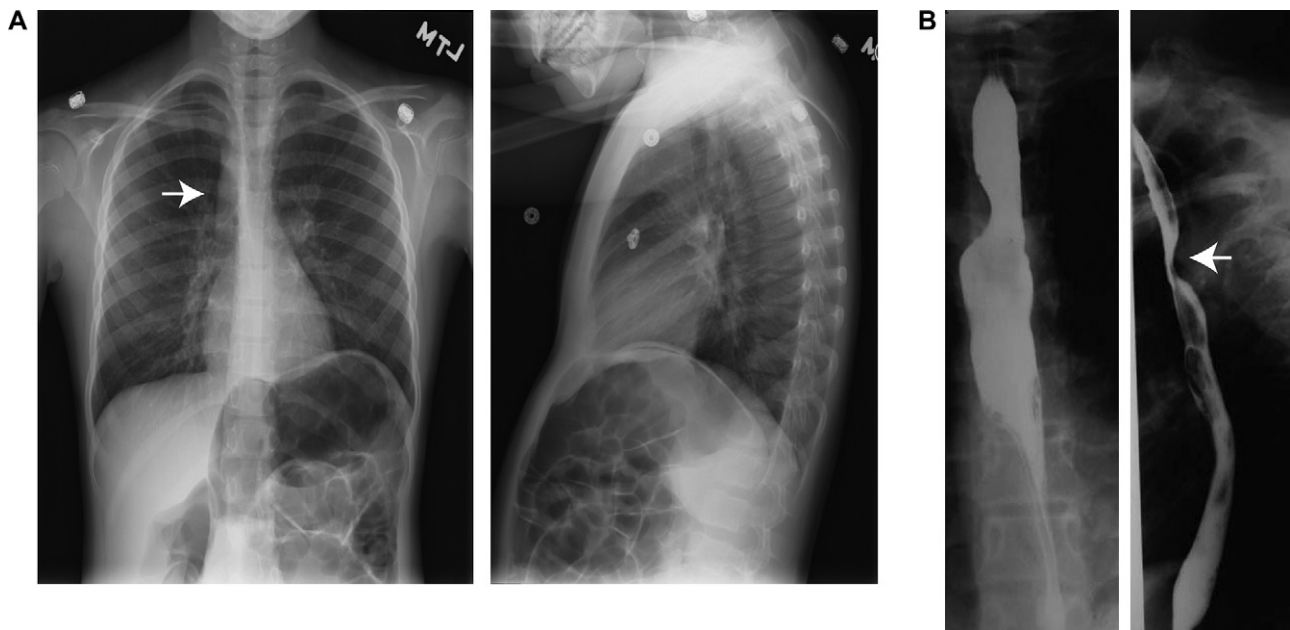


FIG E2. *A, Left panel,* Chest radiograph demonstrating clear lung fields with evidence of a vascular ring with a right-sided aortic arch (*arrowhead*) and absence of a left-sided aortic knob on the PA view. *Right panel,* Lateral chest radiograph demonstrating posterior tracheal narrowing. **B,** Barium swallow demonstrating an esophageal right-sided (*left panel*) and posterior impression (*arrowhead, right panel*) of the esophagus caused by external compression by a vascular ring.

TABLE E1. Age-related differential diagnosis for wheezing

| Condition | Relative frequency of occurrence | | |
|--------------------------------------|----------------------------------|-----------|-------------|
| | Infancy | Childhood | Adolescence |
| Asthma | + | +++ | +++ |
| Airway malacia | ++ | + | — |
| Cystic fibrosis | +++ | + | ± |
| Foreign body | ++ | +++ | ± |
| Airway infection | +++ | ++ | + |
| Bronchopulmonary dysplasia | +++ | + | — |
| Primary ciliary dyskinesia | + | ++ | + |
| Bronchiectasis | + | + | + |
| Congenital anomalies (vascular ring) | +++ | + | — |
| Vocal cord dysfunction | — | ± | ++ |
| Tumors | ± | ± | ± |
| Aspiration syndromes | + | ± | ± |
| Pulmonary edema | + | + | + |

Modified with permission from Chesnick V, Boat T, editors. Kendig's disorders of the respiratory tract in children. 6th ed. Philadelphia: WB Saunders Co; 1998, p. 701.

—, Unlikely to present in this age group; +, likely to present in this age group.